Does Nonsteroidal Anti-inflammatory Drug Use Modify the Effect of a Low-Fat, High-Fiber Diet on Recurrence of Colorectal Adenomas?

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Abstract

The Polyp Prevention Trial was designed to evaluate the effects of a high-fiber (18 g/1,000 kcal), high-fruit and -vegetable (3.5 servings/1,000 kcal), low-fat (20% energy) diet on recurrence of adenomatous polyps. Participants ≥35 years of age, with histologically confirmed colorectal adenoma(s) removed in the prior 6 months, were randomized to the intervention or control group. Demographic, dietary, and clinical information, including use of nonsteroidal anti-inflammatory drugs (NSAID), was collected at baseline and four annual visits. Adenoma recurrence was found in 754 of 1,905 participants and was not significantly different between groups. NSAID use was associated with a significant reduction in recurrence [odds ratio (OR), 0.77; 95% confidence interval (95% CI), 0.63-0.95]. In this analysis, NSAIDs modified the association between the intervention and recurrence at baseline (P = 0.02) and throughout the trial (P = 0.008). Among participants who did not use NSAIDs, the intervention was in the protective direction but did not achieve statistical significance (OR, 0.87; 95% CI, 0.69-1.09). The intervention was protective among males who did not use NSAIDs at baseline (OR, 0.71; 95% CI, 0.54-0.94), but not among NSAIDs users (OR, 1.09; 95% CI, 0.74-1.62). For females, corresponding OR estimates were 1.28 (95% CI, 0.86-1.90) and 2.30 (95% CI, 1.24-4.27), respectively. The protective association observed for NSAID use was stronger among control (OR, 0.63; 95% CI, 0.47-0.84) than for intervention group participants (OR, 0.97; 95% CI, 0.74-1.28). These results should be interpreted cautiously given that they may have arisen by chance in the course of examining multiple associations and Polyp Prevention Trial study participants were not randomly assigned to both dietary intervention and NSAID use. Nevertheless, our results suggest that adopting a low-fat, high-fiber diet rich in fruits and vegetables may lower the risk of colorectal adenoma recurrence among individuals who do not regularly use NSAIDs. (Cancer Epidemiol Biomarkers Prev 2005;14(10):2359–65)

Introduction

The Polyp Prevention Trial (PPT) was a multicenter randomized clinical trial designed to evaluate the effects of a high-fiber (18 g/1,000 kcal), high-fruit and -vegetable (3.5 servings/1,000 kcal), low-fat (20% of total energy) diet on the recurrence of adenomatous polyps in the large bowel. The trial results suggested that the dietary intervention did not influence the risk of recurrence of colorectal adenomas. There was a significant interaction (P = 0.005) between the intervention and gender with a protective association for the intervention among men [odds ratio (OR), 0.89; 95% confidence interval (95% CI), 0.79-1.02]. However, these results did not reach statistical significance (P = 0.11). The recurrence rate among women was moderately higher for intervention participants compared with controls (OR, 1.30; 95% CI, 1.04-1.63; P = 0.03) (1). The PPT investigators later reported that use of nonsteroidal anti-inflammatory drugs (NSAID) reduced the odds of both overall adenoma recurrence (OR, 0.77; 95% CI, 0.63-0.95) and recurrence of advanced polyps (OR, 0.56; 95% CI, 0.31-0.99) (2). This finding was consistent with those reported by randomized trials of adenoma recurrence and results from prospective cohort studies (3, 4).

Several recent studies have suggested that the role of diet, particularly dietary fat, in colon cancer risk may be modified by NSAIDs (5), polymorphisms of the cycloxygenase-2 gene (6), and other lifestyle factors (7). In addition, Hauret et al. (8) reported that NSAIDs modified the effect of physical activity on incident sporadic colorectal adenoma, with inverse effects limited to participants who were nonusers. In this report, we examine whether NSAID use modifies the association of the PPT dietary intervention with adenoma recurrence.

Materials and Methods

Sample Population. The overall design, rationale, dietary intervention, and end point procedures and trial results for the PPT have been reported previously (1, 9-11). Between 1991 and 1994, the study recruited 2,079 males and females, 35 years of age or older, with one or more histologically confirmed colorectal adenomas identified by complete colonoscopy up to 6 months before randomization. Individuals who were more than 150% of their recommended weight, currently using lipid-lowering medications, with surgically resected adenomatous polyps or diagnosed with colorectal cancer, inflammatory bowel disease, or a polyposis syndrome, were considered ineligible. The study was approved by the Institutional Review

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Boards of the National Cancer Institute and each of the eight participating centers and all participants provided written informed consent at entry into the study.

Study Procedures. At baseline and each of four annual follow-up visits, participants provided a fasting blood sample and completed an interviewer-administered questionnaire including demographic, clinical, medication use, and dietary and supplement information. Baseline food frequency questionnaires and 4-day food records were viewed before randomization to ensure that the participants' dietary patterns were not already similar to the intervention plan and to gauge the participants' ability to comply with recording dietary intake data. Following randomization, intervention participants received instruction in the implementation of the PPT high-fiber, high-fruit and -vegetable, low-fat dietary plan, and control participants received printed material on healthy eating. A detailed description of the intervention and the dietary changes achieved has been published previously (9, 11). For the present study, 1,905 participants who completed the full trial follow-up were evaluated.

Dietary Data. Diet was assessed at baseline and annually with a modified Block-National Cancer Institute food frequency questionnaire (12). Prior to the collection of dietary data, participants viewed instructional videos demonstrating food portion size estimates and received instruction in the completion of the dietary instruments. The food frequency questionnaire queried usual food consumption patterns over the past year and was used in the present analysis to create both baseline and dietary change variables.

Assessment of NSAID Use. NSAID use was collected and evaluated in a number of different ways in the PPT, including baseline, ever/never regular use, and consistent use of NSAIDs during the trial as described in detail previously (2). Briefly, at each annual visit, participants were asked about regular medication use (at least once a month). Participants were also asked to bring all currently used prescription and nonprescription medications, including aspirin and nonaspirin NSAIDs such as ibuprofen, naproxen, indomethacin, and piroxicam (not including cycloxygenase-2–specific inhibitor drugs which were unavailable at the time), to each annual visit and information about the name and frequency of use was recorded. Users (ever) were those participants reporting regular use at one or more annual visits. Consistent NSAID users were those reporting regular use at all their annual visits.

Assessment of Adenomas. Participants received full colonoscopies at baseline, at their 1-year visit, and at the end of the trial intervention, ~4 years after randomization. The colonoscopy at the first annual visit allowed for the detection and removal of any lesions missed by the baseline procedure. Recurrent adenomas were those diagnosed and pathologically confirmed between the 1-year visit and the end of trial colonoscopy, inclusive. For participants who completed the baseline but missed the 1-year follow-up colonoscopy, recurrent adenomas were those detected at least 2 years after randomization. A total of 754 participants were found to have recurrent adenomas during follow-up. Biopsy samples of all adenomas removed during colonoscopy were reviewed independently by two pathologists to determine histological features and degree of atypia. Information on the size, number, and location of all lesions detected by colonoscopy was abstracted from endoscopy reports. Advanced adenomas, those generally considered to be more strongly associated with invasive cancer, were defined as one or more of the following: 1 cm or greater, at least 25% villous, or containing any high-grade dysplasia. Nonadvanced adenomas were tubular adenomas with <25% villous component and no high-grade dysplasia.

Statistical Analyses. Statistical analyses were done using Statistical Analysis Systems (SAS) software (13, 14). The characteristics of participants with and without recurrent adenomas were compared by t tests for continuous variables, and χ^2 test for categorical variables. In addition, we also compared users and nonusers of NSAIDs using similar methods. ORs and 95% CIs for the association between adenoma recurrence and outcomes of interest were determined in logistic regression models after adjusting for age and gender. Effect modification by NSAIDs was assessed by including the selected NSAID indicator variable (e.g., baseline, ever/never, consistent) and its cross-product term with the intervention indicator variable in the multivariate model. Statistically significant interactions were observed (e.g., $P = 0.02$ for baseline NSAID use); therefore, analyses were repeated stratified on baseline NSAID use for the intervention effect and stratified on intervention for the association between NSAIDs and adenoma outcomes. In conducting the present analyses, we also observed an interaction between the intervention and gender (as was reported in the trial results). The effect of male versus female for this analysis was a qualitative interaction or a shift in the OR by a constant amount (up for females) and (lower for males). Therefore, we also conducted analyses in which we included the intervention × gender term and used the parameter estimates from the model together with the variance/covariance matrices to calculate the point and interval estimates for the effect of the intervention diet stratified by NSAID use for males and females as separate groups.

We constructed continuous variables to measure dietary change consistent with the intervention goals, regardless of whether the participant was in the intervention or control group. These dietary change variables reflect dietary fat reduction, increased dietary fiber, and increased fruit and vegetable intakes over the trial period. Continuous variables representing the three dietary change categories (fat, fiber, and fruit/vegetable) were then grouped into quintiles based on the distribution among the entire study population without missing end points for entry into models as indicator variables defined by the second through fifth quintiles (greatest improvement) of intake, with the lowest quintile (least improvement) as the reference group. An ordinal score variable was created (i.e., 1, 2, 3, 4, and 5) to conduct linear trend tests across levels of change. For the dietary change variables, effect modification by NSAIDs was assessed by including the selected NSAID indicator variable (e.g., baseline, ever/never, consistent) and its cross-product term with the continuous dietary change variables in separate multivariate models for fat, fiber, and fruit/vegetable intake. A statistically significant interaction was observed for dietary fat change ($P = 0.007$) and, although nonsignificant, the other risk estimates for interactions were in the same direction, and for fruits and vegetables were of a similar magnitude. Therefore, analyses were repeated stratified on baseline NSAID use for the dietary change variables. Analyses were also conducted by gender for the dietary change variables (data not presented).

Lastly, the quintile dietary change variables were combined to create three new variables representing levels of overall improvement. The reference group for overall change was defined as those participants in the lowest quintile (least improvement) for change in fat, fiber, and fruit/vegetable intake. The group with the greatest overall change (most improvement) included those participants in either of the highest two quintiles for change in all three categories of intake. The moderate change group included all those participants remaining, and thus would include participants who may have made significant changes in one or two areas, but not in all three.

In addition to the main analysis evaluating the relationship of the combined effects of the intervention and use of NSAID

use and any adenoma recurrence during the trial, we also evaluated associations with advanced adenoma recurrence in logistic regression models. For advanced adenomas, the comparison group was those with recurrent nonadvanced adenomas or no recurrent adenomas. Associations between selected exposure variables and site of recurrence were evaluated by designating site of recurrence within the bowel as either proximal or distal (including rectal) with the no adenoma recurrence group as the reference in each case.

Potential confounders such as dietary intake of calcium and vitamin D and use of hormone replacement therapy were evaluated by assessing their associations with NSAID use, the intervention, and adenoma recurrence and by comparing models with and without their presence. Final models were adjusted for age and gender. All statistical analyses were two-sided and $P < 0.05$ was considered to be statistically significant.

Results

Descriptive characteristics of study participants by adenoma recurrence status are presented in Table 1. The majority of PPT participants were Caucasian, 64% were male, and most were nonsmokers. Mean age among participants at entry was 61.1 years and mean body mass index was 27.6 kg/m^2. Approximately one third of study participants reported baseline NSAID use and 15% reported consistent NSAID use. At baseline, average energy intake was just over 1,900 kcal/d; participants consumed ~35% of energy as fat and consumed 9.5 g/d of fiber and 2.2 servings/d of fruits and vegetables. In other analyses comparing NSAID users with nonusers (data not presented), NSAID users were more likely to use supplemental calcium and vitamin D compared with nonusers (60% versus 56%, $P = 0.04$, and 55% versus 50%, $P = 0.03$), were older (62.3 versus 60.4 years, $P < 0.001$), and had higher body mass indices (27.9 versus 27.4 kg/m^2, $P = 0.004$). In univariate analyses, NSAID use was not significantly related to baseline energy, fat, fiber, or fruit and vegetable intake. In addition, changes in energy, fat, fiber, and fruit and vegetable intake during trial follow-up were not associated with NSAID use.

We observed a statistically significant interaction between the intervention and NSAID use at baseline ($P = 0.02$) and throughout the trial ($P = 0.008$) with adenoma recurrence. For aspirin use only, the interaction was only significant for the latter ($P = 0.14$ and $P = 0.03$, respectively). In Table 2 we report the results of logistic regression analysis for the effect of the intervention diet on adenoma recurrence stratified by NSAID use, after adjustment for age and gender. Table 2 also includes the results for the effect of the intervention diet stratified by NSAID use for males and females as separate groups, as explained in Materials and Methods. Among all participants who did not use NSAIDs, the effect of the intervention was in the protective direction but did not achieve statistical significance (OR, 0.87; 95% CI, 0.69-1.09). The intervention was protective among male participants who did not use NSAIDs (OR, 0.71; 95% CI, 0.54-0.94), but not among those that used NSAIDs (OR, 1.09; 95% CI, 0.74-1.62) at baseline. For females, the corresponding OR estimates were 1.28 (95% CI, 0.86-1.90) and 2.30 (95% CI, 1.24-4.27), respectively. The results stratified by use of aspirin were similar to those for all NSAIDs, as were results for the associations of both NSAIDs and aspirin with risk for recurrence of advanced adenomas.

In Table 3 we present the results for the association between NSAID use and adenomatous polyp recurrence stratified by intervention status. The protective effect observed for baseline NSAID use was stronger among control group participants (OR, 0.63; 95% CI, 0.47-0.84) than for intervention group participants (OR, 0.97; 95% CI, 0.74-1.28), with stronger results

Table 1. Characteristics of PPT participants by adenoma recurrence*

Characteristic	Overall, n = 1,905	Any polyp, n = 754	No polyp, n = 1,151	P*
Intervention participant (% yes)	50	50	50	0.939
Gender (% male)	64	72	60	0.000
Race (% Caucasian)	90	90	90	0.971
Education (% ≤high school)	25	26	24	0.503
Family history of colorectal cancer (% yes)	27	27	27	0.772
Smoker (% current)	13	14	13	0.693
Multiple adenomas at baseline (% yes)	36	46	30	0.000
NSAIDS, baseline (% yes)	34	31	35	0.106
Consistent trial use (% yes)	15	13	16	0.065
Aspirin, baseline (% yes)	23	22	23	0.551
Consistent trial use (% yes)	10	9	10	0.520
Dose (mg/d)	68.6 (224.0)	56.5 (170.0)	76.4 (253.0)	0.058
Non-aspirin NSAIDS, baseline (% yes)	11	9	12	0.096
Consistent trial use (% yes)	5	4	6	0.037
Supplement Use (any)				
Multivitamin (% yes)	52	49	53	0.098
Calcium (% yes)	57	54	60	0.012
Vitamin D (%yes)	52	48	54	0.018
Age (y)	61.1 (9.9)	62.8 (9.2)	59.9 (10.1)	0.000
Body mass index (kg/m^2)	27.6 (3.9)	27.8 (3.9)	27.4 (4.0)	0.047
Vigorous/moderate activity or both (h/wk)	12.1	12.6	11.7	0.126
Dietary intake at baseline (per day)				
Total energy (kcal)	1,922.4 (582.7)	1,949.6 (609.4)	1,904.5 (564.1)	0.099
Fat (% energy)	35.6 (7.3)	35.2 (7.2)	35.8 (7.4)	0.087
Fiber (g)	9.5 (3.9)	9.5 (4.0)	9.5 (3.8)	0.998
Fruits/vegetables (servings)	2.2 (1.1)	2.2 (1.1)	2.2 (1.0)	0.776
Dietary change (per day)				
Total energy (kcal)	−67.5 (503.0)	−91.8 (528.9)	−51.5 (484.9)	0.090
Fat (% energy)	7.1 (8.7)	6.9 (8.6)	7.3 (8.7)	0.290
Fiber (g)	4.2 (5.9)	4.1 (5.8)	4.2 (6.0)	0.519
Fruits/vegetables (servings)	1.2 (1.4)	1.2 (1.4)	1.2 (1.4)	0.776

*Results presented as means and SDs for continuous variables and % for categorical variables with P values for differences in means determined by t test and differences in proportions determined by χ^2 tests. Adenomatous polyp recurrence diagnosed through postintervention at year 4.7.

Table 2. Effect of a low-fat, high-fiber, high-fruit and -vegetable diet (intervention) on adenoma recurrence by NSAID use overall and in men and women*

		Any adenoma recurrence			Advanced recurrence		
		Control	Intervention	OR (95% CI)	Control	Intervention	OR (95% CI)
		Case/noncase	Case/noncase		Case/noncase	Case/noncase	
NSAID use (baseline)							
No	All	273/372	244/376	0.87 (0.69-1.09)	53/592	42/578	0.80 (0.52-1.22)
	M	200/202	168/238	0.71 (0.54-0.94)			
	F	73/170	76/138	1.28 (0.87-1.90)			
Yes	All	101/201	136/202	1.36 (0.98-1.90)	13/289	17/321	1.25 (0.59-2.64)
	M	79/117	96/128	1.09 (0.74-1.62)			
	F	22/84	40/74	2.30 (1.24-4.27)			
Aspirin use (baseline)							
No	All	299/436	287/445	0.93 (0.75-1.15)	54/681	47/685	0.86 (0.57-1.29)
	M	223/237	194/272	0.76 (0.58-0.98)			
	F	76/199	93/173	1.42 (0.98-2.05)			
Yes	All	75/137	93/133	1.26 (0.85-1.87)	12/200	12/214	0.95 (0.41-2.21)
	M	56/82	70/94	1.08 (0.68-1.72)			
	F	19/55	23/39	1.87 (0.89-3.94)			
Consistent NSAID use							
No	All	334/474	322/492	0.91 (0.74-1.11)	60/748	51/763	0.82 (0.55-1.21)
	M	246/254	221/308	0.73 (0.57-0.94)			
	F	88/220	101/184	1.39 (0.98-1.98)			
Yes	All	40/99	58/86	1.75 (1.05-2.90)	6/133	8/136	1.48 (0.49-4.49)
	M	33/65	43/58	1.46 (0.82-2.62)			
	F	6/34	15/28	3.05 (1.07-8.72)			
Consistent aspirin use							
No	All	346/511	340/526	0.94 (0.77-1.14)	61/796	55/811	0.87 (0.59-1.27)
	M	256/274	230/325	0.75 (0.59-0.95)			
	F	90/237	110/201	1.47 (1.05-2.06)			
Yes	All	28/62	40/52	1.82 (0.97-3.41)	5/85	4/88	0.87 (0.22-3.44)
	M	23/45	34/41	1.73 (0.86-3.45)			
	F	5/17	6/11	2.29 (0.54-9.74)			

*Overall analyses were adjusted for age and gender; gender-specific results were adjusted for age.

seen among those that were consistent NSAID users. Again, similar results were observed for aspirin use and for the associations of both NSAIDs and aspirin with recurrence of advanced adenomas; however, there were small numbers in some cells.

Table 4 presents the results for the association between dietary change (fat, fiber, and fruit/vegetable intake) and risk for adenoma recurrence stratified by NSAID use after controlling for age and gender. Addition of the baseline dietary variables (fat, fiber, and fruit/vegetable intake) did not

Table 3. ORs and 95% CIs of adenomatous polyp recurrence for NSAID use by intervention status*

Group		Any adenoma recurrence		Advanced adenoma recurrence	
		Case/noncase	OR (95% CI)	Case/noncase	OR (95% CI)
Control	NSAIDS use (baseline)				
	No	273/372	1	53/592	1
	Yes	101/201	0.63 (0.47-0.84)	13/289	0.42 (0.22-0.79)
	Aspirin use (baseline)				
	No	299/436	1	54/681	1
	Yes	75/137	0.72 (0.52-1.00)	12/200	0.62 (0.32-1.19)
	Consistent NSAID use				
	No	334/474	1	60/748	1
	Yes	40/99	0.46 (0.31-0.70)	6/133	0.40 (0.17-0.97)
	Consistent aspirin use				
	No	346/511	1	61/796	1
	Yes	28/62	0.50 (0.31-0.81)	5/85	0.50 (0.19-1.29)
Intervention	NSAIDS use (baseline)				
	No	244/376	1	42/578	1
	Yes	136/202	0.97 (0.74-1.28)	17/321	0.68 (0.38-1.23)
	Aspirin use (baseline)				
	No	287/445	1	47/685	1
	Yes	93/133	0.96 (0.70-1.31)	12/214	0.75 (0.39-1.46)
	Consistent NSAID use				
	No	322/492	1	51/763	1
	Yes	58/86	0.89 (0.61-1.28)	8/136	0.78 (0.36-1.69)
	Consistent aspirin use				
	No	340/526	1	55/811	1
	Yes	40/52	0.95 (0.61-1.48)	4/88	0.57 (0.20-1.64)

*Analyses were adjusted for age and gender.

appreciably alter the results and, therefore, these were not included in final models. There was a statistically significant interaction between change in dietary fat intake and NSAID use (P = 0.007). For the other two dietary change variables, fiber and fruit/vegetable intake, the interactions did not reach statistical significance, but the risk estimates were in a similar direction (for fiber, $P_{interaction}$ = 0.46; for fruit/vegetable, $P_{interaction}$ = 0.13). Among participants who did not use NSAIDs, the risk estimates suggest that decreasing fat intake and increasing fiber and fruit and vegetable intake are inversely associated with recurrence of adenomatous polyps.

These analyses were also conducted stratified by gender (data not presented). The results were consistent with those observed for Table 2, with risk estimates suggesting a greater protective association for males who did not report using NSAIDs.

The aggregate variable created to represent three levels of overall dietary improvement was not significantly associated with overall adenoma recurrence; however, there was a suggestion of an inverse association with recurrence of advanced adenomas (OR for the comparison between most improved versus least improved groups, 0.61; 95% CI, 0.34-1.08). Overall, the results of the dietary change analyses suggested a protective effect of dietary changes consistent with the intervention among male participants who did not use NSAIDs.

Discussion

In the PPT, we observed that NSAID use modified the association of a low-fat, high-fiber diet with colorectal adenoma recurrence. Among males who did not use NSAIDs, the dietary intervention was significantly inversely associated with recurrence. We also found that NSAID use was inversely associated with both any and advanced adenomas among participants in the control group.

At least nine randomized, double-blind clinical trials have evaluated the effects of NSAIDs for the prevention of colorectal adenomas. The results are summarized in a recent systematic review by Asano and McLeod (3). Overall, the trial results and results from observational studies are supportive of an inverse association between NSAID use and adenoma recurrence. Aspirin and NSAIDs are thought to lower risk of colon cancer and adenomatous polyps because of their roles as cyclooxygenase (cycloxygenase-1 and cycloxygenase-2) inhibitors, which have the ability to limit the production of prostaglandin E2. Prostaglandins have a wide range of procarcinogenic properties (15).

A number of mechanisms have been proposed for the potential protective effects of low-fat, high-fiber, high-fruit and -vegetable diets on colon cancer risk including direct affects on

Table 4. Effect of dietary change on adenoma recurrence by NSAID use*

Dietary change	Intake range	Case/noncase	OR (95% CI)
NSAIDS nonuser			
Total fat reduction (% kcal)			
Q1	(−24.2 to −0.2)	110/141	1.00
Q2	(−0.2-4.2)	113/137	1.11 (0.77-1.59)
Q3	(4.2-9.1)	104/137	1.00 (0.69-1.43)
Q4	(9.1-14.4)	86/155	0.73 (0.51-1.06)
Q5	(14.4-43.9)	95/164	0.77 (0.53-1.10)
			P_{trend} = 0.10
Dietary fiber increase (g/1,000 kcal)			
Q1	(−19.5 to −0.4)	107/155	1.00
Q2	(−0.4-1.5)	104/143	1.10 (0.77-1.57)
Q3	(1.6-4.7)	102/136	1.14 (0.79-1.63)
Q4	(4.8-8.7)	99/135	1.08 (0.75-1.55)
Q5	(8.8-32.5)	96/165	0.91 (0.63-1.30)
			P_{trend} = 0.76
Fruit/vegetables increase (servings/1,000 kcal)			
Q1	(−3.5-0.0)	117/151	1.00
Q2	(0.1-0.6)	83/150	0.71 (0.49-1.02)
Q3	(0.6-1.4)	124/137	1.26 (0.88-1.78)
Q4	(1.4-2.4)	93/143	0.84 (0.58-1.21)
Q5	(2.4-5.7)	91/153	0.81 (0.56-1.16)
			P_{trend} = 0.02
NSAIDS users			
Total fat reduction (% kcal)			
Q1	(−23.1 to −0.3)	45/78	1.00
Q2	(−0.1-4.1)	34/90	0.65 (0.37-1.12)
Q3	(4.2-9.1)	52/81	1.16 (0.69-1.95)
Q4	(9.1-14.4)	54/81	1.16 (0.70-1.95)
Q5	(14.4-35.3)	48/65	1.42 (0.83-2.44)
			P_{trend} = 0.07
Dietary fiber increase (g/1,000 kcal)			
Q1	(−10.6 to −0.4)	40/73	1.00
Q2	(−0.4-1.5)	46/80	1.09 (0.64-1.88)
Q3	(1.6-4.7)	47/98	0.88 (0.52-1.49)
Q4	(4.7-8.7)	57/74	1.42 (0.84-2.40)
Q5	(8.8-30.4)	43/70	1.16 (0.67-2.02)
			P_{trend} = 0.43
Fruit/vegetables increase (servings/1,000 kcal)			
Q1	(−3.4-0.0)	46/84	1.00
Q2	(0.1-0.6)	33/74	0.74 (0.42-1.29)
Q3	(0.6-1.4)	53/92	1.05 (0.64-1.75)
Q4	(1.4-2.4)	47/76	1.10 (0.65-1.85)
Q5	(2.4-6.4)	54/69	1.50 (0.89-2.51)
			P_{trend} = 0.17

*Analyses were adjusted for age and gender. The reference group for comparison is the quintile that made the least favorable dietary change. $P_{interaction}$ between NSAIDS and the dietary change variables were 0.007, 0.46, and 0.13 for fat, fiber, and fruit/vegetables, respectively.

cell proliferation in the colon, decreased levels of mutagenic substances in the colon, increased stool bulk and dilution of carcinogens, decreased colonic transit time thereby minimizing the exposure to carcinogens, and increased levels of anti-carcinogenic compounds such as antioxidant nutrients and phyto-nutrients thought to be chemopreventive. In contrast to the results for NSAIDs, the results of trials designed to evaluate whether dietary changes affect overall risk of recurrence of colorectal adenomas have been disappointing, providing only limited evidence that dietary changes reduce risk of recurrent colorectal adenomas (1, 16, 17).

We were prompted to conduct an in-depth evaluation of potential effect modification by NSAIDs in the PPT after viewing the results of several recent studies that suggested that the role of diet and diet-related factors in colon cancer risk may be modified by NSAIDs (5). For example, Slattery et al. (5) reported in a large multistate case-control study that high consumption of *trans*-fatty acids increased risk for colon cancer among those that were not using NSAIDs. For NSAID users, colon cancer risk did not increase with increased consumption of *trans*-fatty acids. Wu et al. (18) suggested that beneficial effects of calcium on colon cancer risk observed in their study were only apparent among those who did not use aspirin. Similar findings were observed in a trial where calcium supplementation was more protective among participants who did not use NSAIDs (19). Lastly, Hauret et al. (8) reported that NSAIDs modified the effect of physical activity on incident sporadic colorectal adenoma, with inverse effects limited to participants who were nonusers. Our results are consistent with those reported in the above studies.

One possible interpretation of our results is that the potential for protective effects related to colorectal adenoma recurrence is limited overall, and that once that level is achieved, no further protective effects are observed. This interpretation was proposed by Hauret et al. (8) for their results suggesting an interaction between NSAIDs and physical activity. Another possible consideration is that dietary patterns and NSAID use may affect the absorption, bioavailability, or metabolism of each other. Although residual confounding cannot be ruled out entirely, we found no evidence to suggest that the observed modification of the dietary intervention association by NSAID use was related to increases in other healthy behaviors (e.g., antioxidant, calcium, or vitamin D supplement use, physical activity, or hormone replacement therapy use) among PPT participants who were NSAID users.

We also explored a number of possibilities to explain why our results apparently differ by gender. There was no evidence to suggest that hormone replacement therapy use modified our results. In the PPT there were no intervention status or gender differences in the number of colonoscopies received, nor were there differences in colonoscopies by NSAID use during the trial. We explored whether the intervention diet was implemented differently between men and women and therefore might have influenced the results and found no evidence to this effect. Also there were no differences in hospitalizations or other conditions such as diabetes, pancreatitis, diverticulitis, or gallstones between intervention and control participants. Lastly, we cannot rule out the possibility that the observed differences could be due to chance.

Our findings should be interpreted carefully keeping in mind that we are presenting estimates of relative odds (i.e., ORs) rather than relative risks. We used logistic regression to analyze our data. Logistic regression makes inferences on the odds of a recurrence. It should be emphasized that the odds of a recurrence is not a direct measure of the risk of recurrence when the recurrence is a frequent event (~30% overall proportion of recurrence). However, we believe that the odds is a valid and appealing measure of association in its own right. In addition, a statistical test of whether the OR is equal to 1 (i.e., no association) is a valid test of whether the relative risk is equal to 1.

There are several strengths of this study including the prospective design, the large number of participants available for analysis, and the high-quality and comprehensive outcome data as well as NSAID use, dietary, and supplement data collected throughout follow-up. In addition, participants of the PPT were recruited from a number of clinic locations across the United States. It is possible that this study may not be generalizable to all populations that experience adenomatous polyps. For example, 90% of the PPT participants were Caucasian, the majority completed high school or more education, and all had to meet the health-related eligibility criteria for the trial. Participants with a diagnosed risk factor for colorectal cancer may also be more health conscious than the general population.

In summary, we observed a statistically significant interaction between the PPT intervention and NSAID use on risk for adenoma recurrence. Among male participants not using NSAIDs, there was an inverse association for the intervention with risk for adenoma recurrence. Among control group participants, there was an inverse association between measures of NSAID use and recurrence of adenomas. Additional analyses suggested that dietary changes consistent with the intervention were inversely associated with risk for adenoma recurrence among NSAID nonusers. These results should be interpreted cautiously given that they may have arisen by chance in the course of examining multiple associations. Moreover, PPT study participants were not randomly assigned to both dietary intervention and NSAID use. Nevertheless, our results suggest that adopting a low-fat, high-fiber diet rich in fruits and vegetables may lower the risk of colorectal adenoma recurrence among individuals who do not regularly use NSAIDs.

Appendix 1. The members of the Polyp Prevention Study Group who participated in the conduct of the PPT. However, the data presented in this article and the conclusions drawn from them are solely the responsibility of the above listed coauthors.

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